UNITED STATES DISTRICT COURT
DISTRICT OF MINNESOTA

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| In re: BAIR HUGGER FORCED AIR WARMING DEVICES PRODUCTS LIABILITY LITIGATION | MDL No. 15-2666 (JNE/FLN) |
| This Document Relates To: *All Cases* | **PLAINTIFFS' MEMORANDUM IN SUPPORT OF MOTION TO EXCLUDE THE TESTIMONY OF THEODORE R. HOLFORD UNDER FED. R. EVID. 702** |

## I. INTRODUCTION

The Supreme Court has construed Rule 702 in favor of admitting expert testimony, but there are limits. The proponent of the testimony, whether plaintiff or defendant, has the burden to establish that the expert's testimony is based on a reliable methodology. Failure to show the reliability of each step in an expert's methodology is fatal under Rule 702.

Defendants cannot meet their burden of showing that Dr. Holford's testimony is reliable or relevant. Methodological errors and speculation permeate Dr. Holford's opinions at every step. His unique methodology—to the extent it even exists—is first to disassemble the data in the peer-reviewed, published epidemiological study by McGovern et al., then pluck pieces of data from the study and mix them together with his own post-hoc "reanalysis" of a different data set to concoct a weaker result to suit his conclusion.

Dr. Holford builds his analysis on one factually unsupported premise after another, including: reanalyzing the McGovern study from an incomplete data set; mixing and matching data from other scientific studies and different timeframes; controlling for non-

confounding variables; ignoring the great weight of peer-reviewed literature that contradicts his opinion; failing to follow the methodology he uses outside the courtroom; and declining to conduct his own independent research. Dr. Holford's opinions are so lacking in intellectual rigor that they collapse under the weight of *Daubert* like a house of cards. Because his testimony is neither reliable nor helpful to jurors, it should be excluded.

## II. FACTUAL BACKGROUND

On March 30, 2017, Plaintiffs disclosed the expert report of Jonathan Samet, M.D., M.S., a respected physician, epidemiologist, and public health expert on the issue of general causation. Ex.A, Samet Rpt. Dr. Samet opines that the Bair Hugger Forced Air Warming Blanket ("BairHugger") can cause deep joint infections ("DJI") in exposed patients. Dr. Samet bases his opinion on a recognized approach to evaluating causation, otherwise known as the "sufficient component cause framework." *Id.* at 6–9. He conducted a comprehensive search of relevant scientific literature and reviewed numerous sources of evidence, including the peer-reviewed epidemiological study by McGovern et al.[1] and other published research describing the mechanism of injury—the means by which the BairHugger transmits microorganisms to the surgical field in hip and knee arthroplasties.

The McGovern study was peer-reviewed and published in the JOURNAL OF BONE & JOINT SURGERY in 2011. The investigators compared the infection rates of BairHugger to conductive warming blankets in 1,437 patients at a hospital in England. The study found

[1] P.D. McGovern, *An Investigation of Theatre Ventilation, Patient Warming and Joint Replacement Infection in Orthopaedics*, 93B:11 J BONE & JOINT SURG. 1537-44 (2011).

that use of the BairHugger had a statistically significant increased incidence of DJI (odds ratio: 3.8) compared to the use of conductive blankets. Ex.B, McGovern at 1542 Table II.

On June 1, Defendants disclosed the expert report of Theodore Holford, Ph.D., a biostatistician, to oppose Dr. Samet's general causation opinion. Ex.C, Holford Rpt. Unlike Dr. Samet, Dr. Holford is not a medical doctor. He has no professional experience in the hospital or surgical setting. He does not even have a degree in epidemiology or training in clinical epidemiology. Ex.D, Holford Dep at 13:15-14:12. Tellingly, he failed to perform a routine search of the scientific literature in developing his opinions. *Id.* at 93:11-94:15. Dr. Holford also concedes he lacks expertise to opine on medical or technical issues such as clinical epidemiology, microbiology, air filtration, and the impact of filtration and particles on DJI—all fundamental components of the causation inquiry. *Id.* at 19:22-20:11.

Dr. Holford purported to conduct an "audit" of the McGovern study "in an attempt to reproduce the results" that appeared in the peer-reviewed paper. Ex.C, Holford Rpt. at 2. The source data for Dr. Holford's audit was provided by 3M; it was an incomplete data set that was attached as Exhibit 10 to the deposition of Mr. Mark Albrecht, one of the McGovern study authors. Ex.C, Holford Rpt. at 2. But Dr. Holford did not in fact conduct an "audit" or even attempt to reproduce the results of the study. Based on the draft data set, Dr. Holford employed his own unique methodology of changing the data set for the tally of BairHugger versus conductive blanket infections reported in the study, changing the statistical test the authors used in the study, altering the time periods in which the authors collected data, inserting non-existent confounders to add unnecessary variance to the study,

and then "recalculating" measures of risk for the BairHugger and DJI as reported in the study, ultimately concluding there was no increased risk from the device. *Id.* (passim).

Based on his unique reanalysis of the McGovern study, Dr. Holford concluded that the McGovern study or *any* single epidemiological study cannot support an inference of causation. Ex.C, Holford Rpt. at 6–10. Although drawing causal inference depends on the totality of scientific evidence, Dr. Holford did not consider other sources of relevant medical evidence; he considered only a handful of documents that 3M gave him. Ex.D, Holford Dep. at 94:3–15. Nor did Dr. Holford conduct a search of the relevant literature when he reviewed the Bradford Hill criteria to determine whether the association reported in the McGovern study supported causation. Ex.C, Holford Rpt.at 8–10; Ex.D, Holford Dep. at 93:11-94:15; 275:4–8; 351:17–24; 368:1-371:25; 375:12-376:10. At bottom, Dr. Holford's "expert" opinion is nothing more than litigation driven advocacy for the defense.

## III. LEGAL STANDARDS

Federal Rule of Evidence 702 permits expert witnesses to testify if the subject of their testimony is relevant, the witnesses are qualified to express their opinions, and the evidence upon which they base their testimony is reliable. *Polski v. Quigley Corp.*, 538 F.3d 836, 839 (8th Cir. 2008). Courts are gatekeepers of expert evidence "to make certain that an expert, whether basing testimony upon professional studies or personal experience, employs the same level of intellectual rigor that characterizes the practice of an expert in the relevant field." *Kumho Tire Co., Ltd. v. Carmichael*, 526 U.S. 137, 152 (1999).

Expert testimony must be trustworthy to be reliable. *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579, 590 (1993). That is, the testimony must be appropriately

validated. *Id.* Four nonexclusive factors control the reliability of expert testimony: (1) whether the theory or technique can be and has been tested; (2) whether the technique has been subject to peer review and publication; (3) the technique's known or potential rate of error; and (4) the theory or technique's acceptance within the relevant field. *Id.* at 593–94.

The Eighth Circuit considers additional factors as well: "whether the expertise was developed for litigation or naturally flowed from the expert's research; whether the proposed expert ruled out other alternative explanations; and whether the proposed expert sufficiently connected the proposed testimony with the facts of the case." *Polski*, 538 F.3d at 839. The party seeking admission of expert testimony has the burden of demonstrating its reliability. *In re Baycol Prods. Litig.*, 532 F. Supp. 2d 1029, 1042 (D. Minn. 2007).

A "very significant" criterion of reliability is whether the expert's testimony is based on research independent of litigation. *Daubert v. Merrell Dow Pharm., Inc.*, 43 F.3d 1311, 1317 (9th Cir. 1995) (*Daubert II*). If the proffered expert testimony is not based on independent research, the party proffering it must offer other objective, verifiable evidence and explain precisely how the expert testimony is based on objective sources—a learned treatise, the policy statement of a professional association, a published article in a reputable scientific journal, or the like—to show that the expert followed the scientific method as practiced by (at least) a recognized minority of scientists in the field. *Id.* at 1317–19.

Where the factual basis, data, or the methodology employed by the expert are sufficiently called into question, the court must determine not only if the testimony is reliable, but also whether it has a valid connection to the pertinent inquiry. *Kumho Tire Co.*, 526 U.S. 137 at 149. Expert testimony must therefore "logically advance[] a material

aspect of the proposing party's case." *Daubert II*, 43 F.3d at 1315. The court should not admit opinion evidence "that is connected to existing data only by the *ipse dixit* of the expert," *General Elec. Co. v. Joiner*, 522 U.S. 136, 137 (1997), or that hinges on an expert's unique methodology, *Groobert v. President and Dir. of Georgetown Coll.*, 219 F. Supp. 2d 1, 9 (D.D.C. 2002). Under these circumstances, the court may conclude "there is simply too great an analytical gap between the data and the opinion." *Joiner*, 522 U.S. at 146.

## IV. ARGUMENT

### A. No Recognized Scientific Methodology Exists for Ignoring The Findings of a Published, Peer Reviewed Study that Directly Addresses General Causation

The McGovern article is a published, peer-reviewed epidemiological study that directly investigated the association between DJI and BairHugger. It reported a statistically significant 3.8 fold increased risk of DJI from BairHugger compared to conductive warming blankets. As is routinely done in peer-reviewed literature, the authors described the methods they used and their findings. The article grew out of pre-litigation research, passed peer review, and was published in a respected medical journal; it has never been retracted. Nor has 3M, Dr. Holford, or any other witness called for its retraction. There are no epidemiological studies that contradict or disprove the association between BairHugger and DJI as reported in the study. Publication in a reputable peer-reviewed journal shows the study meets "at least the minimal criteria of good science." *Daubert II*, 43 F.3d at 1318.

Nonetheless, Dr. Holford asserts that the McGovern study is unreliable and does not inform his opinion. He simply dismisses the study and other peer-reviewed research that contradict his opinion. But he does not describe, much less cite, an objectively verifiable

source on causation methodology for his conclusion that a published, peer-reviewed study showing a positive association between BairHugger and DJI merits no weight. Indeed, his analysis is untethered to any recognized scientific method. And his premise—that a study must be free of limitations to be worthy of consideration—is contrary to law and science.

Epidemiologic studies have been well received by federal courts in mass tort suits, both in this judicial district and nationwide. *See, e.g.*, *In re Viagra Prods. Liab. Litig.*, 572 F. Supp. 2d. 1071, 1081 (D. Minn. 2008). In the phenylpropanolamine (PPA) MDL, defense experts attacked a single epidemiologic study showing an association between PPA (a decongestant) and hemorrhagic strokes—the Hemorrhagic Stroke Project ("HSP")—based on a theory similar to Dr. Holford's opinion in this case. *In re Phenylpropanolamine (PPA) Prods. Liab. Litig.*, 289 F. Supp. 2d 1230, 1239 (W.D. Wash. 2003). Just like Dr. Holford, the defense experts there maintained that a single observational study could not show causation and that the HSP study had such serious flaws that it was *per se* unreliable. *Id.* The Honorable Barbara Rothstein, who now heads the Federal Judicial Center, disagreed and gave a name to this meretricious argument: "Defendants' ex post facto dissection of the HSP fails to undermine its reliability. Scientific studies almost invariably contain flaws." *Id.* at 1240 (quoting the REFERENCE MANUAL ON SCIENTIFIC EVIDENCE).

Dr. Holford's testimony in this case meets the same fate. Like the defense experts in the PPA MDL, Dr. Holford goes beyond the defense expert's usual and permissible role of pointing out alleged limitations of a study. He instead declares that a single observational study with "flaws" cannot be considered evidence of general causation, without citing any authority for his position. Ex.C, Holford Rpt. at 2, 7. Not only are Dr. Holford's opinions

on the McGovern study unsupported by the data in Figure 7 of the study, but there is no recognized methodology for how he reaches his opinions. *Daubert II*, 43 F.3d at 1318; *Groobert*, 219 F. Supp. 2d at 9. The Court should therefore bar his baseless opinion that the McGovern study cannot demonstrate an association between the BairHugger and DJI.

### B. Dr. Holford Improperly Reclassified Patient Data in an Attempt to Undermine the Published, Peer-Reviewed Results of the McGovern Study

Testability can be critical to the reliability of expert testimony. *Daubert*, 509 U.S. at 593. This method consists of repeating the experiment to determine whether it produces the same result. Retabulating data based on speculative and unfounded assumptions, cherry-picking variables from different studies ("remixing"), and reanalyzing published data without factual support in order to obtain premeditated results is not valid scientific methodology. *See In re Baycol Prods. Litig.*, 532 F. Supp. 2d at 1046 ("to recalculate a study, based in part on an unreliable methodology, would render the recalculation unreliable"). No matter which expert offers it, opinions based on unsupported speculation are unreliable. *See Glastetter v. Novartis*, 107 F. Supp. 2d 1015, 1045 (E.D. Mo. 2000).

The second error Dr. Holford makes—vitiating the reliability of his approach—is to rely on an incomplete and remixed data set to conclude that the McGovern study does not show a significant difference in DJI rates between BairHugger and conductive warming devices. Ex.C, Holford Rpt. at 2–3. Dr. Holford based his opinion on a data set marked as Exhibit 10 to the deposition of Mr. Albrecht and Exhibit 16 to Dr. McGovern's deposition. *Id.* From the data set in Exhibit 10, as well as selected excerpts of deposition testimony of a few study authors, Dr. Holford contends that one infection in the McGovern study was

miscoded as arising from use of BairHugger instead of conductive blankets. Given that assumption, Dr. Holford retabulated the numbers from Exhibit 10 and concluded that the odds ratio fell from 3.8 to 2.76. *Id.* at 2. Dr. Holford also concluded that his reanalysis eliminated the statistically significant difference in DJI rates between the devices because the p-value rose to .0507, just above the "statistical significance" threshold of .05. *Id.* Dr. Holford's attempt to remix published data is not based in any recognized methodology and fails in the following respects—any one of which is grounds for exclusion under Rule 702.

**1. The Data Dr. Holford Remixed Is Not the Final Study Data.**

One of the perils of acting as a litigation expert is relying on information spoon-fed by counsel. *In re TMI Litig.*, 193 F.3d 613, 628 (3d Cir. 1999). Dr. Holford did not conduct any research; he simply relied on what 3M gave him. Ex.D, Holford Dep. at 94:3–15. Among those documents were Albrecht Exhibit 10 and excerpts of "clarifying deposition testimony" from the McGovern study authors. Ex.C, Holford Report at 2. **However, Dr. Holford admitted he did not know whether Exhibit 10 was the final data set used by the authors in performing their analysis or publishing the paper.** Ex.D, Holford Dep. at 121:24-122:24; 127:22-130:10; 144:15-148:7; 155:8–11; 168:15-170:15; 172:2–24.

At best, all Dr. Holford knew was that the data in Exhibit 10 were incomplete and different from the data reported in the study. *Id.* at 110:13-113:16; 126:18–25. None of the McGovern study authors were able to identify Exhibit 10 as the final data set. For example, when asked if Exhibit 10 contained the final data he analyzed for the paper, Mr. Albrecht testified that there was no way for him "to verify something like this." Ex.E, Albrecht Dep. at 141:22–23. Mr. Albrecht averred that the file he analyzed for the study was different and

contained data that Exhibit 10 lacked. *Id.* at 150:21-151:2. Though Dr. Holford hinged his expert report on Mr. Albrecht's testimony, Dr. Holford tellingly agreed that not even Mr. Albrecht knew whether Exhibit 10 was the final data set. *Id.* at 127:3–7. So how could he?

Ultimately, Dr. Holford conceded that using the wrong or incomplete data would doom his opinion: **"I mean if – if the file is not the correct data, then there – there – there would be a problem with the analysis."** Ex.D, Holford Dep. at 128:12-129:20. He simply assumed, without any corroboration, that the data he manipulated was the same set the study authors relied on for their findings. This unsupported assumption, uncorroborated by the authors, destroys the reliability of Dr. Holford's so-called "expert" conclusions.

**2. Dr. Holford Improperly Speculated that the McGovern Authors Miscounted One DJI as Occurring During the BairHugger Period.**

Dr. Holford also relies on McGovern Exhibit 16 to speculate that "someone erroneously categorized the September 15, 2010 surgery as having used a BairHugger instead of a Hot Dog." Ex.C, Holford Rpt. at 3. Yet Dr. Holford admits he did not know whether the September 15 surgery had been miscoded as to the surgery date or the type of warming device. Ex.D, Holford Dep. at 155:8-11. He just assumed so. More important, **Dr. Holford admits the data sets he relied on—Albrecht Exhibit 10 and McGovern Exhibit 16—excluded a BairHugger infection identified in Figure 7 of the published and peer-reviewed study**. *Id.* at 168:22-170:14. **This admission alone deracinates his conclusions as each and every one of his calculations depends on the incomplete data set contained in Albrecht Exhibit 10 and McGovern Exhibit 16.** *Id.* at 173:13-174:25.

Dr. Holford also misleadingly claims that the study authors agreed that they had misclassified the September 15 surgery as a BairHugger infection. Ex.C, Holford Rpt. at 3. To the contrary, Mr. Albrecht testified that there were no tabulation errors, *see* Ex.E, Albrecht Dep. at 158:21-25, 163:22-24, 167:25-168:12, while Dr. McGovern and Professor Nachtsheim continue to stand by the study, *e.g.*, Ex.F, Nachtsheim Dep. at 350:4–6. To the extent Dr. Reed claimed without explanation that the data included in the study were not the most recent, Dr. Holford agrees with Dr. Reed that adding or subtracting a single DJI ultimately does not impact the "scientific, human, or economic" significance of the published study. Ex.G, Reed Dep. at 43:19-44:9; *cf.* Ex.D, Holford Dep. at 84:8–11.

Equally important, McGovern et al. collected additional data after publication of the study. Based on an even larger population of exposed patients, the authors *again* found that BairHugger significantly increased the risk of infection (odds ratio of 3.6) compared to conductive warming; in fact, the authors found an almost identical risk ratio as reported in the published study. Ex.H, McGovern Dep. at 410:20-415:20; Ex.I McGovern Dep. Ex. 23; *see also* Ex.H, McGovern Dep. at 415:9–20. Dr. Holford not only failed to consider this dispositive evidence, but he admits the updated calculations showing an increased risk from BairHugger contradicts his analysis and conclusions. Ex.D, Holford Dep. at 148:3-5.

All told, Dr. Holford's manipulation of the McGovern study rests on a false foundation. Good scientists would independently verify that the data underlying their calculations are accurate and complete. Dr. Holford did not do so; nor did he consider any deposition testimony contradicting his opinion. In fact, when cross-examined, he admitted that he had no reason to rely on the data sets contained in Albrecht Exhibit 10 or McGovern

Exhibit 16 instead of the published McGovern article or the study author's deposition testimony. *See* Ex.D, Holford Dep. at 172:2–6. He simply cherry-picked data as he saw fit.

Because Defendants have failed to show by a preponderance of evidence that Dr. Holford's methods are reliable, his opinion testimony regarding the retabulation of the McGovern data should be excluded. *In re Baycol Prods. Litig.*, 532 F. Supp. 2d at 1042.

### C. Dr. Holford Unnecessarily and Selectively Applied a Different Statistical Test to Dilute the Strength of the McGovern Study

#### 1. Substituting the Fisher Test for the Chi Squared Test Was Inappropriate.

McGovern et al. performed their statistical analysis using the Chi Squared test, a generally accepted method for calculating risk measurements in epidemiologic studies. They found a statistically significant odds ratio of 3.8 for BairHugger infections compared to conductive warming infections; in other words, more than double the risk of infection.

Instead of applying the Chi Squared test to the "retabulated" McGovern data, Dr. Holford used Fisher's test, which allowed him to calculate a barely non-significant difference in DJI rates between BairHugger and conductive blankets. Ex.C, Holford Rept. at 2. In so doing, Dr. Holford unabashedly agreed to disregarding two "rules of thumb" in biostatistics. First, although application of Chi Squared versus Fisher's test depends on expected values rather than observed values, Dr. Holford admitted to using observed values instead. **His reason for doing so rested on his "own bias" rather than any well-accepted method.** Ex.D, Holford Dep. at 204:5–25. Second, even though the expected value crossed the critical threshold of 5 infections, thus favoring application of Chi Squared, Dr. Holford

blithely rejected the finding and candidly conceded he "didn't follow the rule of thumb." Unhinged from any method, **he "followed [his] own rule of thumb."** *Id.* at 206:17-207:3.

Unable to clean-up his methodological mistake, Dr. Holford alternatively yet confusingly argued that the Chi Square test was not appropriate for "small" sample sizes. Ex.C, Holford Rpt. at 2. Biostatisticians define small sample sizes as less than 1,000.[2] *See* Ex.J, J.H. McDonald, HANDBOOK OF BIOLOGICAL STATISTICS (3d ed. 2014) at 1. The McGovern study included 1,437 patients. By definition, then, the sample size was not "small," so the Chi Squared test was appropriate for calculating statistical significance.

Outside of litigation, Dr. Holford uses the Chi Squared test to analyze even smaller populations, still finding the statistical associations to be important. Ex.D, Holford Dep. at 200:21–23. In a published study on the effect of mold levels on asthma in infants, for example, Dr. Holford used Chi Squared with only 1,002 patients, which he called a "large population," in stark contrast to his newfangled testimony in this litigation. Ex.K, J. Gent, *Levels of Household Mold Associated with Respiratory Symptoms in the First Year of Life in a Cohort at Risk for Asthma*, 110:12 ENV. HEALTH PERSPECTIVES 785 (2002). Using Chi Squared test on this "large" population, moreover, Dr. Holford concluded that mold exposure increases the risk of wheeze and persistent cough in vulnerable infants. *Id.*

[2] Even with "low expected frequencies," notable biostatisticians have found that the Chi Squared test is just as reliable as Fisher's test. *See, e.g.*, F.E. Harrell, Jr., Chair, Biostatistics, Vanderbilt School of Medicine, *Re: [R] Fisher's exact test vs. Chi-square*, R Archives (Sept. 5, 2017), http://tolstoy.newcastle.edu.au/R/help/05/09/11961.html. Still other statisticians, including those whom Dr. Holford respects as experts, refuse to use Fisher's test given its "overly conservative nature." Ex. D, Holford Dep. at 182:13-186:18.

In yet another study, Dr. Holford applied Chi Squared to a population of 982 patients to analyze whether single nucleotide polymorphisms were associated with Non-Hodgkin Lymphoma. Ex.L, A. Hoffman, *Clock-Cancer Connection in Non-Hodgkin Lymphoma*, 69(8) CANCER RES. 3608-09 (2009). The fact that the population was below 1,000 apparently mattered naught despite his testimony in this litigation. Indeed, as a litigation expert, Dr. Holford now discredits the very test that he used in that study. His failure to follow statistical rules of thumb and his radical departure from his practice outside the courtroom reflect litigation bias, not sound science. In sum, he used Fisher's test for one reason and one reason alone: to dilute the significance of the study he was hired to attack.

**2. Dr. Holford's Understanding and Opinion about Statistical Significance is Contrary to Widespread Scientific and Legal Consensus.**

Also misleading is Dr. Holford's testimony that there is not a meaningful difference in DJI rates between BairHugger and conductive blankets. Even assuming, *arguendo*, that he could prove that McGovern et al. erred in tabulating data and in applying Chi Squared to that data, which he cannot, Dr. Holford dismisses any association between BairHugger and DJI that does not reach an arbitrary level of "statistical significance." Ex.C, Holford Rpt. at 2. He routinely yet pedantically maintains that a result that does not reach statistical significance (p-value $\leq .05$) is unreliable *per se* and cannot show causation. *Id.* at 2–4.

Dr. Holford's argument "rests on the premise that statistical significance is the only reliable indicator of causation." *Matrixx Initiatives, Inc. v. Siracusano*, 563 U.S. 27, 40 (2011). "This premise is flawed." *Id.* The Supreme Court has explained that "a lack of statistically significant data does not mean that medical experts have no reliable basis for

inferring a causal link" between a variable and a disease. *Id.* Medical professionals and researchers, moreover, "do not limit the data they consider to the results of randomized clinical trials or to statistically significant evidence." *Id.* Precisely for that reason, it's no secret that courts admit causation testimony based on evidence other than statistical significance. *In re Viagra*, 572 F. Supp. 2d at 1081 (declaring that "persuasive authority" demonstrates that the absence of statistical significance does not detract from reliability).

The scientific community has also denounced the practice of using p-values to draw arbitrary lines of significance. The American Statistical Association warns: "Practices that reduce data analysis or scientific inference to the mechanical 'bright line' rules (such as $p < 0.05$) for justifying scientific claims or conclusions can lead to erroneous beliefs and poor decision making." Ex.M, R Wasserstein, *The ASA's Statement on P-Values*, 70(2) THE AMERICAN STATISTICIAN 131 (2016). The REFERENCE MANUAL agrees, cautioning against the conflation of statistical significance with legal burdens of proof. REFERENCE MANUAL ON SCIENTIFIC EVIDENCE (Federal Judicial Center, 3d ed. 2011) 577 n.81, 578–79.

Dr. Holford's application of Fisher's test to his flawed retabulation of the McGovern data still yields an odds ratio of 2.7—more than a doubling of the risk of DJI from BairHugger use. Ex.C, Holford Rpt. at 2; Ex.D, Holford Dep. at 347:1–3. Yet Dr. Holford insists this figure is meaningless because application of Fisher's test to his mixed and matched data set increases the p-value from .0480 to .0507, thus crossing the artificial line of .05 by "three-thousandths of a decimal point." *Id.* at 211:16–17. Put differently, the odds that the association between BairHugger and DJI cannot be explained by chance decreased from 95.52 times out of 100 to 94.93 times out of 100—a nominal reduction that Dr.

Holford concedes is "not great in magnitude." Ex.C, Holford Rpt. at 2. To say the least, such a *de minimis* difference in statistical significance does not affect the obvious measure of risk. As made clear by the American Statistical Association, no scientist should discard the doubling of risk based on such an artificial difference in p-value. Ex.M, R. Wasserstein, *ASA's Statement on P-Values*, 70(2) THE AMERICAN STATISTICIAN 131 (2016).

**In any event, Dr. Holford accepted that p-values do not "separate real results from false ones" and should "never be used as a substitute for scientific reasoning."** Ex.D, Holford Dep. at 213:23-214:7. He also acknowledged that "reducing data analysis or scientific inference to mechanical bright line rules, such as the p-value of being less than .05 for justifying scientific claims or conclusions, can lead to erroneous beliefs and poor decision making." *Id*. at 214:9–15. That is exactly the case here. Ex.C, Holford Rpt. at 6.

In fact, Dr. Holford's use of such "bright line rules" in this case runs contrary to his academic views. In a paper evaluating intake of polyunsaturated fatty acids and breast cancer risk, Dr. Holford stated: "Although nonsignificant, an association with lower breast cancer risk was observed in premenopausal women." However, this finding was predicated on a p-value of 0.09—well above his bright line rule. Ex.N, S. Goodstine, *Dietary (n-3)/(n-6) Fatty Acid Ratio: Possible Relationship to Premenopausal but Not Postmenopausal Breast Cancer Risk in U.S. Women*," 133 J NUTR. 1409, 1411, 1414 (2003). He then stated that "[t]hese results are consistent with the hypothesis that a higher (n-3)(n-6) PUFA ratio may reduce the risk of breast cancer, especially in premenopausal women." *Id.* at 1409.

Based on any one of the foregoing reasons, Dr. Holford wove his report together with a theory of statistical significance that falls apart with the pull of a single thread. *See*

*Matrixx Initiatives*, 563 U.S. at 40; *Sorensen*, 31 F.3d 638, 649 (8th Cir. 1994) (disavowing backward reasoning to achieve desired conclusions). Indeed, his selective remixing is nothing more than his own "unique methodology" generated for litigation—far from a recognized analytical technique. *See Groobert*, 219 F. Supp. 2d at 9. His unreasoned use of Fisher's test to dilute the findings of the McGovern study should therefore be excluded.

### D. Dr. Holford's Opinions on Hospital Infection Rates and Time Trend Data Do Not Pass Scientific Muster

#### 1. The Wansbeck Hospital Infection Rates Were Not "Out of Control."

Dr. Holford next argues that the McGovern authors collected data from a hospital (Wansbeck Hospital) that was not representative of other hospitals because its infection rates were "out of control." Ex.C, Holford Rpt. at 3–4. Again relying on Albrecht Exhibit 10 instead of the data noted in Figure 7 of the McGovern study, *see* Ex.D, Holford Dep. at 172:12–14, Dr. Holford avers that Wansbeck had a DJI rate of 2.91% from July 1, 2008 to February 28, 2010 (the BairHugger study period), compared to a .60% rate among other hospitals in the area from 2010 to 2015. In calculating the .60% DJI rate, Dr. Holford not only compared apples to oranges by analyzing entirely different time periods, but he failed to control for whether hospitals used conductive warming devices in addition to BairHugger. *Id.* at 239:20-241:10. Without knowing whether the hospitals used different warming devices, **Dr. Holford conceded he could not determine or "know the degree of accuracy" of the calculations in his report.** *Id*. at 242:6–17.

Dr. Holford also failed to consider Dr. Reed's testimony regarding underreporting of survey data. Dr. Reed explained that not every hospital in the U.K. reports as much

infection data as Wansbeck; as a result, the DJI survey data are known to be "low." Ex.G, Reed Dep. at 67:9–15. Government advisors have likewise acknowledged that reported infection rates are unrealistically low due to "poor" surveillance systems. *Id.* Dr. Holford nevertheless assumed the DJI data were totally complete when he conducted his analysis, a fact which he concedes can lead to "data artifact." Ex.O, T. Holford, *Time Trends of Non-Hodgkin Lymphoma: Are they Real?*, 52 CANCER RES. SUPP. 5443, 5446 (1992).

Besides ignoring Mr. Reed's testimony, Dr. Holford turned a blind eye to an analysis of national infection rates prepared by Mr. Albert Van Duren, 3M's 30(b)(6) representative. Mr. Van Duren's graph reveals that national infection rates ranged from 3.8% in 1998 to 5.5% in 2004. Ex.P, Van Duren Dep. Exhibit 77 (3MBH00554267); Ex.Q, Van Duren Dep. at 275:1-276:25. The graph also shows that national joint infection rates were approximately 4.5% during the McGovern study time period—a significantly higher figure than the 2.91% rate at Wansbeck Hospital. Dr. Holford's characterization of Wansbeck Hospital as a "high outlier" therefore amounts to unsupported exaggeration.

**2. Oscillating Infection Rates During the BairHugger Study Period Do Not Impact the Internal or External Validity of the McGovern Study.**

Further disputing the representativeness of Wansbeck Hospital, Dr. Holford splices the BairHugger study period into four quarters to determine whether each quarter had similar DJI rates. Ex.C, Holford Rpt. at 4. Because two quarters of the study period had significantly higher DJI rates than the other quarters, he surmises that such variability "strongly indicates a period in which infections were not controlled." *Id.* at 4–5.

Like Plaintiffs, the Court will not be able to verify whether Dr. Holford correctly calculated the quarterly DJI rates noted in his report because he does not describe his methodology for doing so. He also offers no reason or statistical support for splicing the 3% DJI rate reported in the McGovern study or the moving average shown in Table 2 of his report. He simply assumes, without any scientific basis or other evidence, that DJI rates should and inexplicably do remain constant from quarter to quarter at all hospitals.

What's more, even if the infection rates at Wansbeck were higher in two quarters than for the remaining two quarters, they are not markedly higher than national rates in the United Kingdom, much less the United States. According to Dr. Holford, the first two months at the beginning of 2010 had an 8.41% infection rate, which he claims is 14 times higher than the rate of the National Health Service Hospitals (NHS) in the U.K. Ex.C, Holford Rpt. at 4. Dr. Holford derives the 8.41% figure from the first two months of this period instead of providing the average for the 3-month quarter, thus inflating the rate. He also totally ignores the fact that data sources from the NHS significantly underreport true infection rates. Ex.G, Reed Dep. at 66:1–8. Finally, even the 8% DJI rate he claims demonstrates too much variability does not significantly differ from the 6% rate reported by 3M's corporate witness. Ex.P, Van Duren Dep. Exhibit 77. As a result, Dr. Holford's time trend calculations do not reflect any recognized methodology and thus do not undermine the consistent findings of increased risk of DJI throughout the BairHugger study period. Accordingly, his time trend analysis should be excluded under Rule 702.

**E. Dr. Holford Fabricated His Own Start Date for the McGovern Study**

Dr. Holford also attacks McGovern et al. for choosing the "wrong" start date. He claims the study should have begun 9 months earlier, on October 1, 2007 instead of July 1, 2008, because it would have increased the sample size of the study and thus improved its power. Ex.C, Holford Rpt. at 5. Dr. Holford then reanalyzes the McGovern data by blending it with miscellaneous data from the previous 9 months to conclude that there is no significant difference in DJI rates between BairHugger and conductive blankets. *Id.*

Dr. Holford's alteration of the actual data is not the work of good science. While Dr. Holford claims his opinions are informed by the deposition testimony of the McGovern study authors, he wholly ignores Dr. Reed's testimony, who averred under oath that he began collecting full data on July 1, 2008 instead of October 7, 2007 because Wansbeck had fully transitioned to "full-time surveillance" on July 1, 2008. Ex.G, Reed Dep. at 46:11–20. Dr. Reed further states that there were large data gaps in the months prior to the July 1, 2008 transition period, which would have made data collection prior to then "very unreliable." *Id.* at 64:2–7. **Dr. Holford admits that Dr. Reed's testimony contradicts his time trend analysis, that he had no reason to doubt Dr. Reed's testimony, and that full surveillance began on July 1, 2008.** Ex. D, Holford Dep. at 247:4-249:14. Dr. Holford thus had no choice but to admit that his time trend calculations did not consider the "best data." For purposes of these comparisons, he *sua sponte* created a new time period without a reliable factual basis. Ex.D, Holford Dep. at 226:23-243:25.

Finally, outside the courtroom, Dr. Holford recognizes the importance of collecting data only when complete information becomes available. In a study of the

effect of different indoor heating types on infant respiratory systems, he wrote: "Because of intermittent use patterns of home heating sources, analyzing the data by monitoring period preserves exposure and symptom information that would otherwise be lost by average over the entire winter season. Our analysis is focused on . . . periods for which infant respiratory symptom information is available." Ex.R, E. Triche, *Infant Respiratory Symptoms Associated with Indoor Heating Sources*, 166 AM J RESP. CRITICAL CARE MED. 1105, 1106 (2002). Dr. Holford offers no reason to rely on incomplete data here.

In sum, Dr. Holford reasoned backward to select a start date that would yield his desired result, all the while knowing there were fatal flaws in doing so. Reliance on unfounded assumptions in comparative analysis creates "too great an analytical gap" between his opinion and the data on which it relies. *Junk v. Terminix Intern. Co.*, 628 F.3d 439, 448 (8th Cir. 2010). Dr. Holford's views as to "start date" should be excluded.

### F. Changes in SSI Interventions, Thromboprophylaxis Protocols, and Antibiotic Regimens Did Not Confound the McGovern Study

Dr. Holford further errs in identifying and controlling for nonexistent confounding variables. In violation of clearly-established scientific principles, he remanipulates the incomplete data contained in Albrecht Exhibit 10 to make the significant difference in DJI rates between BairHugger and conductive blankets disappear. Ex.C, Holford Rpt. at 5–6.

The REFERENCE MANUAL ON SCIENTIFIC EVIDENCE defines a "confounder" as a variable that is correlated with both the independent and dependent variables. Thus, "[a]n association between the dependent and independent variables in an observational study may not be causal, but may instead be due to confounding." REFERENCE MANUAL at 285.

Dr. Holford contends that the McGovern study cannot show causation because it did not control for confounders including changes in thromboprophylaxis drugs (tinzaparin to Xarelto), the change in antibiotics (4.5 mg/kg of gentamicin to 3 mg/kg of gentamicin plus 400 mg of teicoplanin), and other interventions to reduce surgical site infections ("SSI bundle") during the study period. Inexplicably, he did not conduct any independent research to determine whether the variables he identified were potential confounders. Rather, he ignored a large body of literature indicating that thromboprophylaxis drugs and antibiotics do not significantly affect DJI rates. Dr. Holford's analysis of confounding is therefore antithetical to basic scientific principles. Because his opinion of confounding "turns scientific analysis on its head," it should be excluded. *See Sorensen*, 31 F.3d at 649.

**1. Interventions to Reduce Surgical Site Infections Are Not Confounders.**

Without mentioning, let alone citing, a single scientific study, Dr. Holford guesses that other infection controls implemented at Wansbeck Hospital as part of an SSI bundle confounded the McGovern study. Ex.C, Holford Rpt. at 4. Dr. Holford's failure to cite a single study is not surprising, for there are no published peer-reviewed studies showing that interventions to reduce surgical site infections affect DJI rates. To the contrary, the literature shows that such changes do not significantly affect DJI rates. *See, e.g.*, Ex.H, McGovern Dep. at 408:17-409:25. For example, Wansbeck Hosptial switched from standard wound dressings to the "Jubilee" dressing in the middle of the McGovern study. The only peer-reviewed study on point found that DJI rates were not significantly different among patients who received either dressing. *See* Ex.S, McGovern Ex. 22. Faced with these facts, Dr. Holford unequivocally admitted that he did not "separately

study" the impact of "SSI intervention measures" on DJI. Ex.D, Holford Dep. at 367:15-368:2. Nor was he even able to define "SSI" despite his admission that surgical site infections were "not the same thing" as deep joint infections. *See id*. at 304:13-306:10.

To the extent Dr. Holford's report actually cited two online articles, which are not published peer-reviewed studies, they both focus on surgical site infections rather than the outcome of interest in this litigation, *to wit*, deep joint infections. Ex.C, Holford Rpt. at 4 n.9 & n.10. The first article discusses strategies to reduce "SSI" but emphasizes that "Mr. Reed's studies with tiny air bubbles on a mock-up theatre proved that forced air warming interferes with the laminar flow from the clean air canopy." *Id.* at 4 n.9. It never says that SSI controls significantly impact DJI rates. The second online article, notably entitled "Implementing Effective *SSI* Surveillance," does not either. *See id.* at 4 n.10.

Even if Dr. Holford had cited published studies to support his views, it would not matter. **Dr. Holford leaves no question that the impact of SSI controls on DJI rates are "beyond the scope of [his] opinion."** *Id.* at 4. **If that were not enough to dispose of his opinion, he made clear at his deposition that he has "no scientific basis or expertise" to conclude that SSI controls impact DJI rates and thus confounded the McGovern study**. Ex.D, Holford Dep. at 306:17-308:14. The Court should therefore bar Dr. Holford's opinion testimony regarding the impact of SSI measures on the study.

**2. Every Single Published Study Demonstrates that Thromboprophylaxis Drugs Cannot Be Reliably Ruled In as a Confounder.**

Dr. Holford relies on a single study to argue that the change in types of thromboprophylaxis (anticoagulant) drugs used before surgery—tinzaparin and

rivaroxaban (Xarelto)—confounded the McGovern study. Ex.C, Holford Rpt. at 5–6; Ex.T, C. Jensen, *Return to theatre following total hip and knee replacement, before and after the introduction of rivaroxaban*, 93-B(1) J BONE & JOINT SURGERY Br., 93-B, 1 (2011). However, the Jensen study did not find statistically significant differences in DJI rates from using Xarelto versus tinzaparin; rather, it reported that the infection rates for both are "similar." *Id.* at 91. **Because the Jensen study does not support Dr. Holford's conclusion, he admits the scientific literature does not suggest a relationship between thromboprophylaxis drugs and DJI**. Ex.D, Holford Dep. at 293:7-295:13. Without an *a priori* basis to draw a relationship between the two, this eviscerates his "expert" conclusion.

Moreover, four separate randomized controlled trials—also known as the RECORD trials—found no difference in infection rates between Xarelto and enoxaparin, a low molecular weight heparin nearly identical to tinzaparin. All four trials followed thousands of patients randomized to Xarelto, enoxaparin, and placebo to study the safety of these thromboprophylactic drugs in orthopedic surgeries, including the incidence of infection. *See* Ex.U, B. Eriksson, *Rivaroxaban versus Enoxaparin for Thromboprophylaxis after Hip Arthroplasty*, 358(26) N. ENGL. J. MED. (2008); Ex.V, A. Kakkar, *Extended Duration Rivaroxaban versus Short-Term Enoxaparin for the Prevention of Venous Thromboembolism after Total Hip Arthroplasty*, 372 LANCET 31-39 (2008); Ex.W, M. Lassen, *Rivaroxaban versus Enoxaparin for Thromboprophylaxis after Total Knee Arthroplasty*, 358(26) N. ENG. J. MED. (2008); Ex.X, A. Turpie, *Rivaroxaban versus Enoxaparin for Thromboprophylaxis after Total Knee Arthroplasty (RECORD 4)*, 373 LANCET 1673-80 (2009). And all four randomized controlled trials found a non-significant

difference in infection rates between Xarelto and enoxaparin. Dr. Holford ignores each and every one of these trials despite their obvious relevance. This, too, disproves his opinion.

If that were not enough to exclude his opinion, Dr. Holford entirely ignores the deposition testimony of the McGovern study authors and a more recent study by Jameson and Reed, which analyzed 13,000 patients and concluded that Xarelto does not significantly increase the risk of DJI. Ex.Y, S. Jameson, *Wound Complications Following Rivaroxaban Administration*, 94 J BONE JOINT SURG. AM. 1554-8 (2012). Given that study, Professor Nachtsheim and Dr. Reed both testified that the change from tinzaparin to Xarelto did not confound the McGovern study. Ex.F, Nachtsheim Dep. at 347:7-348:1; Ex.G, Reed Dep. at 215:7–18. Dr. Holford, in contrast, concedes he has not reviewed the scientific literature regarding the relationship of Xarelto and DJI. Ex.D, Holford Dep. at 295:2–8. Nor is he aware of any literature suggesting a nexus between the two. *Id.* at 295:9–13. His failure to review the universe of adverse information—ranging from the foregoing testimony, to the four RECORD trials, to the Jensen and Jameson studies—directly belies his treatment of thromboprophylaxis drugs as confounding variables. *See, e.g.*, *Tyree v. Boston Scientific Corp.*, 54 F. Supp. 3d 501, 519 (S.D.W. Va. 2014) (collecting cases).

In addition to sweeping over unfavorable information, Dr. Holford does not offer any sound reason for mixing and matching inclusion criteria from two different studies (*i.e.*, the McGovern and Jensen studies) in order to construct his own remixed estimate of confounding. Ex.C, Holford Rpt. at 5–6. But even if Dr. Holford had a valid reason, **he admits that his calculation has not been published and is "not a very good estimate."**

Ex.D, Holford Dep. at 219:1-23; 294:24-295:1. He also admits that his calculations are less reliable than those in the McGovern study—the very study he attacks. *Id.* at 221:22-222:3.

Dr. Holford compounds his error by controlling for this non-confounding variable. Ex.C, Holford Rpt. at 6. While he relies on a textbook by Breslow and Day[3] to justify his method, *id.* at 8–9 n.14, he fails to heed its criteria for treating a variable as a confounder: "[I]f a variable C is *known from other studies* to be related to disease . . . then C should be treated as a confounding variable." Ex.Z, Breslow at 107. As explained above, nary a study has identified a relationship between Xarelto—or any other anticoagulant for that matter—on DJI rates. It stands to reason that by "[c]ontrolling for type of thromboprophylactic drug in this case," Dr. Holford violates the very authority that he cites. Ex.C, Holford Rpt. at 6.

Breslow & Day also recommend that because "good evidence may be available from previous studies that C is not causally related to the disease . . . it should not be incorporated as a confounding factor." Ex.Z, Breslow at 105. Outside the courtroom, Dr. Holford follows the rules, arguing that "one can lose precision by unnecessarily adjusting for a covariate" when the variable is known to be associated with exposure but not itself independently related to disease. Ex.AA, T. Holford, *Confounding in Epidemiologic Studies*, 45 BIOMETRICS at 1320 (1989). Leery to dispute his own teaching, **Dr. Holford admitted at his deposition that his attempt to control for Xarelto during the McGovern study period created a loss of precision.** Ex.D, Holford Dep. at 293:7-294:23.

[3] N. Breslow, *Statistical Methods in Cancer Research*, [p. 103-107] (Int'l Agency for Research on Cancer, Lyon FR 198).

Not to mention Dr. Holford's additional admission that he relied on the incomplete data contained in Albrecht Exhibit 10 when conducting those calculations. *Id.* at 174:3–7.

By inserting a false confounder without an *a priori* basis, Dr. Holford deliberately created imprecision in the data he manipulated. This is not good science and renders the conclusion drawn from it inadmissible. *In re Baycol Prods. Litig.*, 532 F. Supp. 2d at 1046.

**3. Dr. Holford Admits the Change in Antibiotics is Not a Confounder.**

Dr. Holford also manufactured another false confounder—the change in antibiotics used during the McGovern study—to argue that BairHugger does not increase DJI rates. Dr. Holford surmises that the change from gentamicin to a combination of gentamicin and teicoplanin during the McGovern study period could account for the drop in DJI rates after Wansbeck transitioned from BairHugger to conductive warming. Ex.C, Holford Rpt. at 6.

Like his prior opinions, Dr. Holford's testimony on antibiotic regimens is anathema to relevant scientific literature. A recent study by Hickson and Reed finds "no clear benefit to using one particular antibiotic agent/regimen" versus another in orthopedic surgeries. Ex.BB, C. Hickson, *Prophylactic Antibiotics in Elective Hip and Knee Arthroplasty*, 4 BONE JOINT RES. 101, 186 (2015). Another paper often cited by 3M agrees. Ex.CC, A. Melling, *Effects of Preoperative Warming on the Incidence of Wound Infection After Clean Surgery*, 358 LANCET 876, 876 (2001) ("The value of prophylactic antibiotics in clean-contaminated and contaminated surgery is not contentious but the benefits of prophylactic antibiotics in reducing wound infection rates after clean surgery remain unclear.").

Although Dr. Holford apparently still believes that the change in antibiotic could have confounded the McGovern study, he paradoxically concedes that it did not

significantly affect DJI rates. Ex.C, Holford Rpt. at 6. Professor Nachtsheim, a statistics professor at the University of Minnesota, reached the same conclusion after reviewing data comparing DJI rates among patients who received gentamicin compared to gentamicin plus teicoplanin. Ex.F, Nachtsheim Dep. at 332:20-339:25; Ex.DD, Nachtsheim Dep. Exhibit 27. Professor Nachtsheim concluded that DJI rates were not significantly different after use of either protocol. Ex.F, Nachtsheim Dep. at 333:16-335:11. After controlling for the second protocol, moreover, he also testified that DJI rates were still significantly higher among BairHugger patients. *Id.* at 335:15-339:7. Professor Nachtsheim thus concluded that there was no statistical basis to conclude that antibiotics were a confounding factor because there was no significant difference between the patients who received either regimen. *Id.* at 339:8-17; *see also id.* at 349:22-23 ("I'm confident that those weren't confounding factors."). This conclusion coheres with simple science. As Dr. Reed testified, bacteria produce biofilm on joint prosthetics that "protect [the bacteria] from antibiotic and other mechanisms the body might have to rid the infection." Ex.G, Reed Dep. at 184:8–12.

**Because the change in antibiotic protocols did not meaningfully affect the change in DJI rates, as Dr. Holford concedes, there is no basis for him to control for this variable as a confounder in his analysis**. Ex.D, Holford Dep. at 321:22-322:14. If anything, Dr. Holford realizes that the change in antibiotic created "reverse" or "negative" confounding by artificially lowering the DJI rate during the BairHugger period of the McGovern study. *Id.* at 317:2–6. Put simply, accepting Dr. Holford's calculations, the risk of BairHugger warming is even greater than the 3.8 odds ratio reported by McGovern. Ex.C, Holford Rpt. at 6 (calculating higher DJI rate from gentamicin plus teicoplanin than

gentamicin). His testimony regarding antibiotics as confounders should thus be excluded under Rule 702. *See* REFERENCE MANUAL at 595 (if disease incidence rates do not vary substantially when comparing the variable in both groups, the variable is not a confounder).

**4. Dr. Holford Improperly Controlled for Both the Thromboprophylaxis Protocol and the Antibiotic Regimen in His "Confounder" Reanalysis.**

Although Dr. Holford could not reliably identify the change in thromboprophylaxis drugs or antibiotics as confounding variables, he proceeded to control for both variables. Ex.C, Holford Rpt. at 6; Ex.D, Holford Dep. at 324:17–19. Based on this scientifically improper and underpowered calculation, Dr. Holford proclaims that "all of the difference in risk is accounted for by these two confounding variables." Ex.C, Holford Rept. at 6.

To be sure, Dr. Holford knows that unnecessarily controlling for nonconfounding variables results in inaccurate and insignificant estimations of risk. His own publications state as much. Ex.AA, T. Holford, *Confounding in Epidemiologic Studies*, 45 BIOMETRICS 1309, 1320. He also knows that controlling for both variables would cut the patient population in half, yet he failed to perform a rudimentary power analysis. Ex.D, Holford Dep. at 324:17-325:15; Ex.E, Albrecht Dep. at 217:23-218:4; Ex.F, Nachtsheim Dep. at 340:5-11. In fact, **Dr. Holford confessed that his calculation creates twice as much unpredictability as the study he was hired to attack**. Ex.D, Holford Dep. at 325:8-326:1.

Altogether, Dr. Holford first distorted the McGovern data by relying on incomplete data sets and then manufactured two nonconfounding variables. From this faulty premise, he erred yet again by controlling for both of these variables, using a method he disavowed outside of litigation, in a deliberate attempt to reach his desired outcome of showing no

increased risk of infection. The Eighth Circuit has wholly rejected this type of backwards reasoning. *Sorensen*, 31 F.3d at 649. For these reasons, Dr. Holford's unsupported obfuscation of non-existent confounding variables is not only unreliable but inadmissible.

### G. Dr. Holford Should Not Be Permitted to Address General Causation Because He Did Not Properly Apply Recognized Causation Methodology

Finally, Dr. Holford's testimony on general causation fails under Rule 702 because he did not follow generally accepted methods for evaluating potentially causal relationships. Indeed, he failed to follow any clear method other than his own *ipse dixit*.

After an epidemiological study finds an association, epidemiologists look at the totality of evidence and consider several factors to guide their judgment about whether the association and the additional evidence reflect a true causal relationship. REFERENCE MANUAL at 598–99. One generally accepted set of factors is the "Bradford Hill" criteria, which include: temporal relationship; strength of association; dose-response relationship; biological plausibility (coherence with existing knowledge); consideration of alternative explanations; cessation of exposure; specificity; and consistency with other knowledge. *Id.* at 596–600; *In re Viagra Prods. Liab. Litig.*, 572 F. Supp. 2d 1071, 1081 (D. Minn. 2008). Given those fact-based criteria, the REFERENCE MANUAL ON SCIENTIFIC EVIDENCE makes clear that, "[i]n the end, deciding whether associations are causal typically is not a matter of statistics alone, but also rests on scientific judgment." REFERENCE MANUAL at 222.

In stark contrast to Dr. Samet's analysis, the fatal flaw in Dr. Holford's methodology is that he limited his causation analysis to just that—statistics. Ex.C, Holford Rpt. at 1–10; Ex.D, Holford Dep. at 17:13–14. **In fact, Dr. Holford conceded that he based his opinion**

**on statistics alone, even though he admitted that drawing causal inferences "is not a matter of statistics alone."** Ex.D, Holford Dep. at 374:7-376:10. He did not perform any independent investigation or consider the arc of relevant scientific literature; he relied on only 19 documents provided by 3M. *Id.* at 93:11-94:15; 275:4-8; 295:9-13; 351:17-352:1.

Given this scientific slip, Dr. Holford never considered the mechanism of injury, including studies showing that the BairHugger increases particles and bacteria in the sterile surgical field, thereby increasing the risk of DJI in orthopedic patients. *See* REFERENCE MANUAL at 664-665. Assessing the biological plausibility of an association "depends upon existing knowledge about the mechanisms by which the disease develops." *Id.* at 604. When such evidence exists, "it lends credence to an inference of causality." *Id.* **Unlike Dr. Samet, Dr. Holford concedes he did not consider how the BairHugger causes infection and that he is not qualified to offer an expert opinion on the subject.** Ex.D, Holford Dep. at 340:15-23; 351:22-352:1; 368:3-11. **He "leaves it to others to discuss this evidence further" since it is "beyond [his] area of expertise."** Ex.C, Holford Rpt. at 9.

Dr. Holford has also failed to investigate even the most rudimentary of matters, including how the BairHugger works. When confronted with publications about the device and the impact of airborne particles on DJI, **Dr. Holford averred it was "not [his] area."** Ex.D, Holford Dep. at 370:11-371:22. At the same time, however, Dr. Holford agreed that mechanistic data on how BairHugger and similar devices disrupt airflow "coincides with a lot of the concern" regarding the impact of BairHugger on DJI. *See id.* at 371:18-372:12.

At the end of the day, Dr. Holford has no basis to testify about general causation. He is a statistician without any medical training, let alone a degree in epidemiology. His

lack of expertise and failure to consider relevant mechanical and biological data create "too great an analytical gap" between his "expert" opinion and the limited data he relies upon. *Joiner*, 522 U.S. at 146. The Court should exclude Dr. Holford's general causation opinion.

## V. CONCLUSION

For the reasons stated above, the Court should exclude the testimony of Dr. Holford.

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